

EDITORIAL

Clinical & Experimental Allergy

Re-defining food allergy phenotypes and management paradigm: is it time for individualized egg allergy management?

This editorial discusses the findings of Clark, et al. [18] pp. 706–712.

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Current management of food allergy reflects a changing landscape. In recent years, we have begun to appreciate that different phenotypes of hen's egg white and cow's milk allergy exist and are associated with different prognoses [1]. Epidemiologic data suggest that the age of the patient, concurrent atopy, and allergens involved are significant to the prognosis [2]. About 80% of children become tolerant to egg and milk, while only 20% of children become tolerant to peanut [2]. Studies based on general paediatric populations suggest that most children outgrow milk and egg allergies by school age [2, 3]. In contrast, among children with multiple food allergies evaluated at a referral centre, many had persistent egg and milk allergy well into their teenage years [4, 5]. The longer a food allergy persists, i.e. into late teenage and early adult years, the less likely the patient will become tolerant [2].

Investigational studies have also provided evidence for distinct phenotypes of food allergy. Children who generate IgE antibodies directed predominantly to conformational epitopes of ovomucoid in egg white and caseins in cow's milk are likely to have transient allergy, while those with IgE antibodies directed predominantly at sequential epitopes are likely to have a more persistent allergy [6, 7]. Such laboratory tests are not yet utilized outside of research, but have the potential to be useful in clinical diagnosis and prognosis.

In studies that confirmed the tolerance of extensively heated (baked) products by means of supervised oral food challenges, approximately 80% of egg- and milk-allergic

children were able to safely include baked goods to their diet [8, 9]. Ingestion of baked goods had no negative effect on growth or intestinal permeability. Mechanistic studies demonstrated that the introduction of baked egg and milk was associated with decreasing skin prick test (SPT) weals and increasing food-specific IgG4 antibody levels [8, 9]. In the milk study, there was a transient increase in CD25⁺Foxp3⁺T regulatory lymphocytes [10]. These changes are similar to the changes associated with oral food immunotherapy and suggest that baked egg and milk in the diet might promote the development of tolerance to unheated egg and milk [11].

These data support the notion that a more individualized approach to egg and milk allergy is possible. Considering that strict dietary avoidance of egg and milk is difficult, associated with a risk for nutritional deficiencies, and negatively affects the quality of life (QOL) for the entire family, introduction of baked products containing egg or milk would be a significant improvement. The unresolved question remains: what is the right approach to accomplish this?

The British Society for Allergy and Clinical Immunology (BSACI) has recently published recommendations for home reintroduction of well-cooked (baked) egg [12]. These guidelines advocate home reintroduction of well-cooked egg (e.g. cake) at age 2–3 years and if tolerated then lightly cooked egg (e.g. scrambled egg) at age 3–4 years in patients with a history of mild symptoms to a significant exposure of egg who do not suffer from active asthma. These new BSACI guidelines raise several questions without answers supported by evidence. The first is how to identify appropriate candidates for home reintroduction. Can we reliably predict the severity of a reaction and how to categorize those with no history of exposure but positive test results? There are no widely accepted criteria for categorizing a food allergy as mild, moderate, or severe. Severity may be assigned based on symptoms and as such, prior food-induced anaphylaxis does seem to

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mark an increased risk for future severe reactions, although fatal food-induced anaphylaxis has been reported in subjects without prior severe reactions [13, 14]. Practicing allergists often take into account both the symptoms and the amount of allergen ingested that triggered a reaction. Others consider treatment as a sign of severity, such as if epinephrine was used; however, the use of specific medications depends on whether the parent or the physician is treating, availability of medications, and/or interpretation of signs and symptoms. The severity of a reaction depends on multiple factors including the amount of allergen ingested, food preparation, the presence of an acute illness, underlying chronic disease, alcohol consumption, anti-acid medications, and exercise [15, 16]. Commercial laboratories typically assign a severity 'class' to specific IgE levels; however, the levels are not comparable across foods and are useful only for predicting the likelihood that an individual would react if the allergen were ingested, not what type of symptoms or reaction will occur [17].

In a study published in this issue, Clark et al. [18] report the results of a longitudinal study of 95 egg-allergic children. The authors interpret their results as supporting evidence for the BSACI guidelines. The subjects were able to tolerate well-cooked egg (sponge cake baked at 180 °C for 20 min) at a median age of 5.6 years (range 2–13.2 years) and uncooked egg (uncooked pasteurized frozen whole egg nuggets) at 10.3 years (range 2–15.2 years), thus confirming prior observations that tolerance to well-cooked egg precedes the development of tolerance to unheated egg. The cohort had a median onset of allergy at 12 months (IQR 8–13 months), a low incidence of prior anaphylaxis to egg (7%), low egg-specific IgE levels (median 2 kU/L; IQR 0.6–6.80 kU/L), and small to moderate SPT weal (median 4 mm; IQR 2–5 mm). These characteristics likely biased the

population to consist mainly of subjects with mild egg allergy. Indeed, epinephrine was not used during any food challenge, although nine subjects experienced respiratory symptoms during uncooked egg challenges and three received nebulized bronchodilators. In a cohort of children with presumably more severe egg allergy, it was difficult to predict based on history or testing who would tolerate baked egg [8]. Furthermore, 19% of baked egg (muffin)-reactive subjects and 23% of baked egg-tolerant but lightly cooked egg (French toast)-reactive subjects experienced mild anaphylaxis that was treated with intramuscular epinephrine. This argues against the notion that tolerance of baked egg products reliably predicts milder reactions to lightly cooked egg and highlights the differences in the management of mild anaphylaxis that exists in the international allergist community.

There is mounting evidence that adding well-cooked/baked egg to the diets of egg-allergic children can be accomplished and would improve the QOL and nutrition. Data from research studies support that the addition of well-cooked egg may shorten the time to resolution of egg allergy. As exciting as these findings are, these patients must be carefully selected. New guidelines in the United States by the NIAID (National Institute of Allergy and Infectious Diseases)-sponsored expert panel have not incorporated the introduction of well-cooked egg into the management of egg allergy [19]. Considering that the access to an allergy specialist and availability of oral food challenges vary widely among centres and countries, the study by Clark et al provides a valuable insight into individualizing and simplifying management of children with mild egg allergy [18]. However, in our opinion, we have not fully defined the phenotypes and reliable markers of mild egg allergy, and thus have not validated the safety of home introduction of well-cooked/baked egg.

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